

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 12

REMARKS

The present response is intended to be fully responsive to all points of objection and/or rejection raised by the Examiner and is believed to place the application in condition for allowance. Favorable reconsideration and allowance of the application is respectfully requested.

Applicants assert that the present invention is new, non-obvious and useful. Prompt consideration and allowance of the claims is respectfully requested.

Status of Claims

Claims 1-38 and 40-71 are pending. Claims 3-5, 7, 9, 19, 21, 32-38, 40, 42, 44, 49-62, 64 and 65 have been withdrawn. Claims 6 and 45 have been cancelled without prejudice or disclaimer. In making this cancellation without prejudice, Applicants reserve all rights in these claims to file divisional and/or continuation patent applications. Claims 1 and 2 have been objected to. Claims 1, 2, 6, 8, 10-18, 20, 22-31, 43, 45-48, 63 and 66-71 have been rejected. Claims 1, 2 and 66 have been amended. The amendments to claim 1, 2 and 66 are editorial in nature. Claims 1 and 2 have been further amended. Support for the amendments to claims 1 and 2 can be found on page 2, [0014]-[0016] of the Application as published. Applicants respectfully assert that no new matter has been added.

Double Patenting Rejections

In the Office Action, the Examiner provisionally rejected claims 1, 2, 6, 8, 10, 14 and 16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-26 of copending Application no. 10/473,180.

Applicants will provide a terminal disclaimer upon indication by the Examiner of allowable claims.

In the Office Action, the Examiner provisionally rejected claims 1, 2, 6, 8, 10-13, 18, 20, 22-24 and 26-30 under the judicially created doctrine of obviousness-type double

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 13

patenting as being unpatentable over claims 13, 18, 19, 24, 29 and 30 of copending Application no. 11/204,391.

Applicants will provide a terminal disclaimer upon indication by the Examiner of allowable claims.

In the Office Action, the Examiner rejected claims 1, 2, 6, 8, 10-18, 20 and 22-31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 6, 16, 17, 19 and 20 of US Patent No. 7,655,445 (claims refer to US Application no. 10/986,058 as the published patent is not immediately available in the database).

Applicants will provide a terminal disclaimer upon indication by the Examiner of allowable claims.

Claim Objections

In the Office Action, the Examiner objected to claims 1 and 2 because of alleged informalities. Claims 1 and 2 have been amended in order to cure these informalities. Claim 66 has been similarly amended. Accordingly, Applicants request withdrawal of the objection.

CLAIM REJECTIONS

35 U.S.C. §102 Rejections

The Examiner has rejected claims 1, 2, 8, 10, 13-17, 67 and 68 under 35 U.S.C. §102(b), as being anticipated by Pikas (IDS dated 26 December 2006).

Claim 1 is directed to a method of preparing a sulfated polysaccharide capable of binding to a protein, consisting of stepwise enzymatically treating an unsulfated or incompletely sulfated polysaccharide with a mixture of enzymes, said mixture of enzymes consisting of *N*-deacetylase-*N*-sulfotransferase (NDST), optionally eparitinase; optionally an epimerase; at least one *O*- sulfotransferase selected from a group consisting of 2-OST, 6-OST, 3-OST; optionally $\Delta^{4,5}$ glycuronidase; wherein the order of the enzymatic steps can be varied and wherein said method comprises at least one in vitro step.

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 14

Claim 2 is directed to a method of preparing heparan sulfate, consisting of stepwise enzymatically treating an unsulfated heparan synthon or incompletely-sulfated heparan sulfate precursor with a mixture of enzymes, said mixture of enzymes consisting of N-deacetylase-N-sulfotransferase (NDST); optionally heparitinase; optionally an epimerase; at least one O- sulfotransferase selected from a group consisting of 2-OST, 6-OST, 3-OST; optionally $\Delta^{4,5}$ glycuronidase; wherein the order of the enzymatic steps can be varied and wherein said method comprises at least one in vitro step.

Claim 6 has been cancelled.

Claims 8, 14, 15 and 67 depend from and incorporate the limitations of claim 1.

Claims 13, 16, 17 and 68 depend from and incorporate the limitations of claim 2.

Claims 1 and 2 have been amended to introduce the language “consisting of” rather than “comprising.” With the amendment to claims 1 and 2, Applicants believe that claims 1 and 2 as amended exclude any non-enzymatic, chemical sulfation modifications as would be clear for any person of ordinary skill in the art and that Pikas does not demonstrate a complete enzymatic method of preparing a sulfated polysaccharide capable of binding to a protein. Furthermore, the chemical modifications of Pikas are not selective and result in a population of molecules which have a variety of alterations, unlike the specific enzymatic activity disclosed by the present invention. Therefore, Pikas does not anticipate claims 1 and claims 8, 14, 15 and 67 which depend therefrom, nor claim 2 and claims 13, 16, 17 and 68 which depend therefrom. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner has rejected claims 1, 2, 6, 8 and 10 under 35 U.S.C. §102(b), as being anticipated by Toida *et al.* (PTO-892, Ref. U).

Claims 1 and 2 have been amended. Claim 8 depend from and incorporate the limitations of claim 1. Claims 9 and 10 depend from and incorporate the limitations of claim 2. Claim 6 has been canceled.

Toida is directed to the preparation of oligosaccharides from heparin by partial depolymerization using heparin lyase (page 32040, first paragraph). Toida does not perform

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 15

any enzymatic synthesis comprising stepwise treating an unsulfated or incompletely sulfated polysaccharide with enzymes, wherein the enzymes consists of N-deacetylase-N-sulfotransferase (NDST), optionally heparitinase and optionally C-5 epimerase. At least one OST is selected form the group consisting of 2-OST, 6-OST, 3-OST, Optionally $\Delta^{4,5}$ glycuronidase. Therefore, Toida does not anticipate claims 1 and 2 and claims 8 and 10 which depend therefore. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The Examiner has rejected claims 1, 2, 6-10, 13-17, 67 and 68 under 35 U.S.C. §102(b), as being anticipated by Wei *et al.* (of record).

Claims 1 and 2 have been amended. Claims 8, 14, 15 and 67 depend from and incorporate the limitations of claim 1. Claims 9, 10, 13, 16, 17 and 68 depend from and incorporate the limitations of claim 2. Claim 6 has been cancelled.

Wei only teaches one step in the sulfation of a polysaccharide, i.e. the N-deacetylation-N-sulfation of the N-position of the glycosidic residue. The resulting incompletely sulfated polysaccharide is not epimerized and/or O-sulfated. Therefore, Wei *et al.* does not anticipate claim 1 and claims 8, 14, 15 and 67 which depend therefrom and claims 2 and claims 9, 10, 13, 16, 17 which depend therefrom. Accordingly, Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §103 Rejections

The Examiner has rejected claims 6, 11, 12, 18, 20, 22-31, 46, 47, 69 and 70 under 35 U.S.C. §103(a), as being unpatentable over Pikas (IDS dated 26 December 2006) and further in view of Habuchi *et al.* (of record), in view of Koeller (PTO-892, Ref. V), in view of Toone *et al.* (PTO-892, Ref.W).

Claims 1 and 2 have been amended. Claims 11, 46 and 47 depend from claim 1 and claim 12 depends from claim 2. Claims 18, 20, 22-31, depend both from claims 11 and 12. Claim 69 depends from claim 11 and claim 70 depends from claim 12. Claim 6 has been cancelled.

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 16

As discussed above, claims 1 and 2 and claims 11, 12, 18, 20, 22-31, 47, 47, 69 and 70 which depend from and/or incorporate the limitations of claims 1 and 2 are not anticipated by Pikas. As stated by the Examiner, the teachings of Pikas differ from the instantly claimed invention in that O-sulfation of the polysaccharide was accomplished chemically rather than enzymatically.

Applicants assert that the prior art references cited alone or their combination do not teach or suggest a "method of preparing a sulfated polysaccharide capable of binding to a protein, comprising stepwise treating an unsulfated or incompletely sulfated polysaccharide with enzymes, wherein said enzymes consists of: N-deacetylase-N-sulfotransferase (NDST), optionally heparitinase, optionally C-5 epimerase, at least one OST selected form a group consisting of 2-OST, 6-OST, 3-OST, optionally $\Delta^{4,5}$ glycuronidase, wherein the order of the enzymatic steps can be varied and wherein said method comprises at least one in vitro step" (Emphasis added).

Applicants assert that Pikas teaches a sulfation process that is primarily chemical. Habuchi teaches the in vivo activity of the various enzymes. Koeller refers only to the enzymatic synthesis of an unsulfated or incompletely sulfated polysaccharide using glycosyltransferases (page 1158) and does not refer to epimerases or O-sulfotransferases. Toone *et al.* teaches the enzymatic synthesis of saccharide monomers and of some saccharide oligomers (schemes 2-20) and does not refer to epimerases or O-sulfotransferases. Since Koeller and Toone do not describe the activities of epimerases and of O-sulfotransferases and since Habuchi and Pikas (and Koeller and Toone) do not teach the stepwise enzymatic in vitro synthesis of sulfated polysaccharides, Pikas, Habuchi, Koeller and Toone alone or in combination do not render obvious Applicants claimed invention.

Further, a stepwise, in-vitro, enzymatic process such as the method disclosed claims 1 and 2 is not obvious in view of a corresponding *in-vivo* process. This is because *in vitro* synthetic parameters such as temperature, pH, reaction times, concentrations, atmosphere, and ingredients must be carefully selected in order for each step to work. Therefore, it would not be obvious for a person of ordinary skill in the art to look at the *in-vivo* process described by Habuchi and to try to perform such process *in-vitro*. A person of ordinary skill in the art, when looking at Pikas would not be motivated to try the enzymatic process of the present

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 17

invention because Pikas mainly uses chemical steps instead of enzymatic ones. Note that even though Pikas does have access to NDST (pages 304 and 305), Pikas prefers to use a chemical N-deacetylation and N-sulfation step thus teaching away from attempting an enzymatic process.

Accordingly Pikas in view of Habuchi, Koeller and Toone, does not render obvious Applicants' invention. Therefore, Applicants respectfully request withdrawal of the rejection.

The Examiner has rejected claims 43, 45 and 48 under 35 U.S.C. §103(a), as being unpatentable over Pikas (IDS dated 26 December 2006) and further in view of Habuchi (of record), in view of Koeller (PTO-892, Ref. V), in view of Toone (PTO-892, Ref. W) and further in view of van Boeckel (PTO-892, Ref. X), in view of Kusche (of record), in view of Nader (of record) and in view of Myette (of record).

Claims 43 and 48 depend from and incorporate the limitations of claim 1. Claim 45 has been cancelled.

As discussed above, claim 1 is not rendered obvious over Pikas and claims 43 and 48 which depend from and incorporate the limitations of claim 1 are therefore not rendered obvious by Pikas.

Claim 45 has been cancelled rendering the rejection to this claim moot.

Applicants believe that as discussed above, Pikas in view of Habuchi, Koeller and Toone does not render obvious Applicants claimed invention. Van Boeckel, Kusche, Nader and Myette do not cure the deficiencies of Pikas, Habuchi, Koeller and Toone as Van Boeckel, Kusche, Nader and Myette do not disclose a stepwise, enzymatic *in vitro* sulfation process that consists of the epimerases and *O*-sulfotransferases as does the present invention. Therefore Pikas in view of Habuchi, Koeller, Toone, Van Boeckel, Kusche, Nader and Myette do not render obvious Applicants' claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

The Examiner has rejected claims 63, 66 and 71 under 35 U.S.C. §103(a), as being unpatentable over van Boeckel *et al.* (PTO-892, Ref. X), in view of Kusche *et al.* (of record),

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 18

in view of Pikas (IDS dated 26 December 2006) in view of Habuchi *et al.* (PTO-892, of record), in view of Nader *et al.* (of record), in view of Myette *et al.* (of record), in view of Koeller *et al.* (PTO-892, Ref. V) and in view of Toone *et al.* (PTO-892, Ref. W).

Claim 63 is directed to an in vivo enzymatic method of producing pentasaccharaide 15. Claim 66 is directed to an enzymatic method of synthesizing pentasaccharide 15 wherein said method comprises at least one in vitro step.

Claim 71 depends from and incorporate the limitations of claim 66.

Applicants believe that as discussed above, Pikas in view of Habuchi, Koeller and Toone, can not render obvious Applicants claimed invention. van Boeckel, Kusche, Nader and Myette do not cure the deficiencies of Pikas, Habuchi, Koeller and Toone, i.e. van Boeckel, Kusche, Nader and Myette do not disclose a stepwise, enzymatic *in vitro* sulfation process that consists of the epimerases and *O*-sulfotransferases as does the present invention. Therefore, van Boeckel *et al.* in view of Kusche *et al.*, Pikas, Habuchi *et al.*, Nader *et al.*, Myette *et al.*, Koeller *et al.* and Toone *et al.* can not render obvious Applicants claimed invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants assert that the pending claims are allowable. Their favorable reconsideration and allowance is respectfully requested.

Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below. Similarly, if there are any further issues yet to be resolved to advance the prosecution of this application to issue, the Examiner is requested to telephone the undersigned counsel.

APPLICANT(S): ROSENBERG, Robert D.

SERIAL NO.: 10/722,587

FILED: November 28, 2003

Page 19

Please charge any fees associated with this paper to deposit account No. 50-3355.

Respectfully submitted,

/Mark Cohen/

Mark S. Cohen
Attorney/Agent for Applicant(s)
Registration No. 42,425

Dated: July 6, 2010

Pearl Cohen Zedek Latzer, LLP

1500 Broadway, 12th Floor

New York, New York 10036

Tel: (646) 878-0800

Fax: (646) 878-0801